REMARKS

Upon entry of the amendment, claims 2-8, 39-43, and 45-65 are pending in the present application. No new matter has been added.

Claim objection

Claims 2, 3, 5-8, and 39-65 are objected to for containing non-elected subject matter. As required by the Office, these claims have now been amended to be drawn to the elected species, SEQ ID NO: 2. This objection may therefore be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Written Description

Claims 2, 3, 5-8, and 39-65 are rejected as being inadequately described. In applying this rejection, the Office asserts that the specification fails to provide specific structural and functional features for the claimed polypeptides, or alternatively, fails to provide a representative number of polypeptides containing a sequence with at least 90% sequence identity to SEQ ID NO: 2 and having the ability to modulate NFκB signaling pathway.

As amended, claim 2, from which claims 3, 5-8, 39-43, and 45-52 depend, and claim 53, from which claims 54-65 depend, are now directed to methods of modulating NFκB activity by contacting cells with polypeptide agents containing the extracellular domain of a TRADEα polypeptide and having the ability to modulate the activity a TRADEα polypeptide. The extracellular domain may have at least 95% sequence identity to amino acids 1-168 of SEQ ID NO:2, or alternatively, may be encoded by a polynucleotide that hybridizes under stringent conditions to the complement of nucleotides 1-504 of SEQ ID NO:1. Because the claims now

recite a specific structural and functional relationship for the polypeptide agents to be employed in the claimed methods, on this basis alone this rejection should be withdrawn.

Turning to the Office's assertion that the specification fails to provide a representative number of TRADEα polypeptides, Applicants disagree and submit that more than one species of TRADEα polypeptides falling within the limitations of the claims are in fact described in the present disclosure. On this point, Applicants direct the Office's attention to page 133, lines 8-24 of the specification, Figure 9, and Figure 14A, in which various, different TRADEα polypeptides (e.g., Flag-TRADEα, Flag-TRADE 1-368, Flag-TRADE 1-328, Flag-TRADE 1-218, and Flag-TRADE 1-196) having the ability to modulate NFκB activity are disclosed. Thus, Applicants have not only provided a structural and functional relationship for the polypeptides useful in the claimed methods, but have also provided a representative number of species for such polypeptides.

In view of the foregoing, Applicants assert that one skilled in the art reading the specification would immediately understand the claimed subject matter. Accordingly, one skilled in the art would understand that any polypeptide agent containing the extracellular domain of a TRADEα polypeptide would be useful for modulating NFκB signaling activity, as is claimed. Applicants therefore respectfully request that this rejection be withdrawn.

Enablement

Claims 2, 3, 5-8, 39-65 are rejected for lack of enablement on two asserted grounds. First, the Office states that the specification fails to provide any working examples, as it "fails to teach any fusion proteins or polypeptides comprising the extracellular domain of TRADE, or polypeptides comprising a segment that shares 90% sequence identity to the extracellular domain

can activate or inhibit NFκB signaling." Second, the Office asserts that the specification fails to teach how to use the claimed method, by failing to teach any disease resulting from TRADE disregulation, for example. For the reasons outlined below, each of these bases for the rejection are respectfully traversed.

Turning to the first ground of rejection, Applicants point out that, contrary to the Office's assertion, the specification provides, not only one, but rather multiple examples of polypeptides containing the extracellular domain of a TRADEα polypeptide that can modulate the activity of NFκB. As discussed above, Applicants have conducted a study, in which various constructs encoding for TRADEα deletion mutants(e.g., Flag-TRADEα, Flag-TRADE 1-368, Flag-TRADE 1-328, Flag-TRADE 1-218, and Flag-TRADE 1-196) were co-expressed with the NFκB promoter-driven luciferase reporter construct. Because each of these polypeptides contains a TRADEα extracellular domain and was shown to modulate NFκB promoter-driven luciferase activity, these TRADEα polypeptides clearly fall within the limitations of the present claims. Thus, Applicants have provided various examples of TRADEα polypeptides containing a TRADEα extracellular domain and having the ability to modulate NFκB signaling.

Referring to the experiment described above however, the Office questions the predictability of the claimed invention based on Applicants'conclusion that it is the intracellular domain (a.a 169-417 of SEQ ID NO:2), rather than the extracellular domain, that is involved in the activation of NFκB (see page 133, lines 21-22 of the specification). Applicants note that this conclusion, while correct, does not question the predictability of the claimed invention. In the experiment described above, Applicants generated TRADEα polypeptides by deleting various portions of the intracellular domain. Because the expression of these polypeptides – TRADEα polypeptides having aberrations in the intracellular domain - causes a modulation in NFκB

signaling, the intracellular domain clearly has a role in NFκB signaling. Conversely, these TRADEα polypeptides all contain a TRADEα extracellular domain, as is required by the present claims. Thus, the experiment relied on by the Office does not render the claim invention unpredictable. This aspect of the rejection should therefore be withdrawn.

Turning now to the second basis of the § 112 rejection, the Office asserts that the specification fails to provide a patentable use for the claimed peptide. More specifically, the Office states that the specification fails to disclose any disease resulting from the misexpression of TRADE or teach the nexus between the claimed method, the modulation of NFκB, and the modulation of TRADE. Applicants disagree.

As discussed above, Applicants' disclosure clearly establishes a nexus between the claimed method, the modulation of NFκB, and the modulation of TRADE. Because Applicants successfully modulated NFκB transcription using various TRADEα polypeptides, one skilled in the art reading the specification would immediately understand that modulating the NFκB signaling pathway would merely require contacting a cell with TRADEα polypeptides, such as those found in Applicants' disclosure.

Moreover, one skilled in the art would also understand that the claimed invention would be useful for treating and preventing any disease that would benefit from the modulation of TRADEα activity, or alternatively, from the modulation of NKκB signaling. Diseases that would benefit from modulation of TRADE activity are described in the specification, for example, at page 26, line 22 through page 27, line 2 and include, for example, inflammatory diseases, cancer (e.g., lung or prostate), Crohn's disease, and cardiovascular diseases. Furthermore, diseases that would benefit from modulation of NFκB signaling were well known in the art at the time of filing and are described, for example, in Baldwin et al. (J. Clin. Invest.

107: 3-6, 2001, submitted herewith as Exhibit A). One skilled in the art reading the present specification would immediately understand that the claimed method would be useful for the treatment and prevention of any of these diseases.

Applicants further submit that, contrary to the Office's assumption, one skilled in the art seeking to make and use the claimed invention may not necessarily contact a cell with the claimed polypeptide agent solely for therapeutic purposes. On this point, Applicants direct the Office to page 19, lines 20-25 of the specification, which states:

> The present invention provides for methods of modulating TRADE activity, e.g., in a cell or in vitro for the purpose of identifying agents that modulate TRADE expression and/or activity, as well as both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant TRADE expression or activity or a disorder that would benefit from modulation of TRADE expression and/or activity.

Thus, one skilled in the art reading the specification would understand that, in addition to therapeutic and prophylactic uses, the present invention would also be useful for the purpose of identifying agents that modulate TRADE expression or activity. One skilled in the art would further understand that such screening methods would merely require using techniques taught in the specification and/or known in the art. M.P.E.P. § 2164.01(c) states that "if *any* use is enabled when multiple uses are disclosed, the application is enabling of the claimed invention."

Applicants submit that such requirement has been met, and withdrawal of the § 112, first paragraph rejection is respectfully requested.

For the foregoing reasons, Applicants submit that the present specification provides ample, enabling guidance to those skilled in the art seeking to practice the currently claimed methods. Accordingly, the § 112, first paragraph rejection for lack of enablement should be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 2, 3, 5-8, and 39-65 are rejected as being indefinite. Claims 2, 3, 5-8 and 39-52 are rejected for reciting "a polypeptide agent that modulates the activity of a TRADEα polypeptide comprising a TRADEα polypeptide." The Office asserts that it is unclear which polypeptide Applicants are referring to. Applicants have amended these claims to clarify the claim language. This aspect of the rejection should be withdrawn.

Claims 6-8 and 39-41 are rejected as indefinite for reciting the term "mature". As amended, the term "mature" no longer appears in the claims, thereby rendering this aspect of the rejection moot.

Claims 53-65 are rejected as indefinite for reciting "said polypeptide agent inhibits the activity of a TRADEα polypeptide sequence." The Office states that, while the activity of a polypeptide may be inhibited, the activity of a polypeptide cannot be inhibited. Applicants have amended claim 53, from which the other rejected claims depend, according to the Examiner's suggestion. This aspect of the rejection should be withdrawn.

Claims 59-62 are rejected for reciting "soluble form of the TRADEα polypeptide sequence is a TRADEα-Fc fusion protein" because it is unclear how a polypeptide sequence can be a fusion protein. Applicants have amended the claim to clarify the claim language.

In view of the foregoing amendments and comments, reconsideration and withdrawal of the rejection for indefiniteness is requested.

Applicants submit that the application is in condition for allowance, and such action is respectfully requested. Enclosed is a request for continued examination and a check in payment of the required fee.

Applicants have further enclosed a petition for extension of time and a check in payment of the required fee. Although no additional charges are believed to be due, the Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to the undersigned's account, Deposit Account No. 50-0311, Ref. No. 22058-569.

Respectfully submitted,

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EXHIBIT A

PERSPECTIVE SERIES

NF-κB in defense and disease

Albert S. Baldwin, Jr., Series Editor

SERIES INTRODUCTION

The transcription factor NF-κB and human disease

Albert S. Baldwin, Jr.

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Beginning with its discovery in 1986 and continuing through the present, the transcription factor NF-κB has attracted widespread interest based on its unusual regulation, the variety of stimuli that activate it, the diverse genes and biological responses that it controls, the striking evolutionary conservation of structure and function among family members, and its apparent involvement in a variety of human diseases (Table 1). Importantly, and consistent with the last point, NF-κB has been shown to be the target of several anti-inflammatory and anticancer drugs.

Discovered by David Baltimore's group (1), NF-κB was shown to be ubiquitously expressed and regulated in an unusual manner in that it could be activated by phorbol esters in the presence of protein synthesis inhibitors. The basis for this type of regulation ultimately was shown to involve the interaction of NF-κB with an inhibitor protein known as IκB (reviewed in refs. 2, 3). Cloning of the NF-κB subunits has revealed a family of proteins exhibiting a conserved central region known as the Rel homology domain, which is involved in DNA binding, interactions with IκB molecules, and dimerization. There are presently five members of the immediate NF-κB family in mammals: p50/p105, p65/RelA, c-Rel, RelB, and p52/p100. The p50 and p52 proteins are derived from precursor proteins or by cotranslational mechanisms from the appropriate mRNA. Although many dimeric forms of NF-κB have been detected, the classic form of NF-κB is the heterodimer of the p65/RelA and p50 subunits. The cloning of the first form of IκBα was facilitated by the observed homology between it and the COOH-terminal region of the p105 of NF-κB (2). Other forms of IκB have been identified, including IκBβ and IκBε (3). IκBβ interacts with similar NF-κB subunits, but its degradation is specifically associated with persistent NF-κB activation (3). An interesting member of the IκB family is Bcl-3, which functions through interactions with certain NF-κB subunits to promote transcription (2, 3). Three proteins related to NF-κB have been identified in *Drosophila*. These are Dorsal, Dif, and Relish, which are involved in expression of genes controlling dorso-ventral patterning in development and the fly immune response. *Drosophila* has an IκB homologue known as Cactus, whose interactions with Dorsal are under control of Toll, a homologue of the IL-1 receptor (2, 3).

NF-κB can be activated within minutes by a variety of stimuli, including inflammatory cytokines such as TNF-α and IL-1, T-cell activation signals, growth factors, and stress inducers. The activation of NF-κB is normally associated with induction of phosphorylation of IκB, followed by its degradation by the proteasome and nuclear translocation (2, 3). Recently, a kinase complex know as the IκB kinase (IKK) has been identified that, when activated, phosphorylates IκBα on serines 32 and 36 (reviewed in ref. 4). Additionally, NF-κB regulation involves phosphorylation of NF-κB subunits, promoting transcriptional activity (see ref. 3). In the nucleus, NF-κB binds to target DNA elements and positively regulates the transcription of genes involved in immune and inflammatory responses, cell growth control, and apoptosis. Genes encoding cytokines, cytokine receptors, cell adhesion molecules, chemoattractant proteins, and growth regulators are positively regulated by NF-κB (Table 2). Genes regulated by NF-κB include those encoding IL-2, IL-6, IL-8, the IL-2 receptor, the IL-12 p40 subunit, VCAM-1, ICAM-1, TNF-α, IFN-γ, and c-Myc (2, 3). Consistent with the regulation of genes involved in the immune and inflammatory response, mice null for several of the NF-κB subunits show defects in clearing bacterial infection along with defects in B- and T-cell functions (see ref. 3). Surprisingly, the knockout of the p65/RelA subunit dies at day 16 of development from extensive liver apoptosis, revealing a role for NF-κB in controlling cell death (5). One can also assume that there is redundancy in the NF-κB system, since the combined p50 and p52 knockout showed osteopetrosis with a block in osteoclast differentiation, whereas the individual p50 or p52 knockouts show no such defect (6, 7).

The ability of NF-κB to be activated by inflammatory cytokines such as TNF-α and to regulate genes involved in inflammatory function raised the question of whether NF-κB dysregulation would be asso-

Table 1
Some diseases associated with NF-κB activation

Atherosclerosis	Diabetes
Asthma	Euthyroid sick syndrome
Arthritis	AIDS
Cachexia	Inflammatory bowel disease
Cancer	Stroke

Table 2
Some disease-related genes regulated by NF-κB

Cyclin D1	Cancer
IL8	Asthma
MCP1	Atherosclerosis
MMP9	Cancer, arthritis
c-Myc	Cancer
5′ deiodinase	Euthyroid sick syndrome
HIV LTR	AIDS
Bcl-xL	Cancer
c-IAP2	Cancer
iNOS	Septic shock
Cox2	Inflammation, colorectal cancer

LTR, long terminal repeat.

ciated with inflammatory disease. Indeed, as discussed by Tak and Firestein (this Perspective series), NF-κB is activated in the inflamed synovium of rheumatoid arthritis patients (8) as well as in the synovium of animal models of this disease (9). Interestingly, inhibition of NF-κB inhibited the inflammation in a bacterial cell wall model for arthritis (9). The fact that NF-κB regulates TNF-α expression and is a key effector of this cytokine is consistent with the development of therapies aimed at blocking TNF as a therapy for rheumatoid arthritis. NF-κB activation is assumed to lie at the heart of other inflammatory diseases, such as asthma (1), and has been shown to be required for development of inflammatory bowel disease in an animal model (10). Thus, the ability of NF-κB to activate transcription of genes encoding cell adhesion molecules (ICAM-1, VCAM-1, E-selectin) and chemoattractant proteins (monocyte chemoattractant protein-1 [MCP-1]) would lead to the recruitment of inflammatory cells to the lung, a hallmark of asthma (11). Additionally, NF-κB appears to be an effector, downstream of TNF-α, in euthyroid sick syndrome (12) and in cachexia (13). The Perspective by Tak and Firestein in this series focuses on the role of NF-κB in inflammatory disorders, whereas the Perspective by Zhang and Ghosh focuses on the key role of NF-κB in promoting innate immune responses. These two articles clearly illustrate the "good and evil" aspects of NF-κB whereby NF-κB is required for immunological mechanisms but detrimental when it is dysregulated.

Consistent with its essential role in inflammation, NF-κB is known to be the target of anti-inflammatory compounds (see ref. 11). Thus, it has been reported that aspirin and other nonsteroidal anti-inflammatory drugs block NF-κB (14–16). Glucocorticoids such as prednisone have been shown to block NF-κB activation by different mechanisms in different cell types (11, 17). In fact, other anti-inflammatory compounds used in therapy have been shown to inhibit NF-κB. For example, gold compounds used as antiarthritic therapies were shown to block NF-κB activation (18). The development and use of NF-κB inhibitors in a variety of disorders are the subject of the Perspective by Yamamoto and Gaynor.

Many of the same issues regarding NF-κB activation and inflammation can be extended to NF-κB and its potential involvement with atherogenesis. NF-κB is known to be activated in endothelial cells by oxidized LDLs (19) and by fluid shear stress (20), key initiating and progression mechanisms in the process of atherosclerosis. Recruitment of monocytes and their extravasation into the subendothelial space is a key event in atherogenesis (21) and is likely to be regulated by NF-κB, as is the induction of proliferation of vascular smooth muscle cells (22). Consistent with these in vitro studies are results showing that NF-κB is activated in the atherosclerotic lesion (23). The complex issues surrounding a potential role of NF-κB in atherogenesis will be dealt with in depth by Collins and Cybulsky in this Perspective series. Interestingly, dietary compounds that are known to block the initiation of atherogenesis, as well as other diseases such as cancer, are now known to inhibit NF-κB activation (for example, see ref. 24).

One of the earliest observations regarding NF-κB was that it is a transcriptional regulator of HIV (reviewed in refs. 2, 3). Two NF-κB sites in the HIV long terminal repeat (LTR) have been proposed to be involved in viral transcription and replication (25). Interestingly, it has been reported that HIV infection induces NF-κB activation, which may suppress HIV-induced apoptosis in infected myeloid cells (26). Many other viruses have coopted NF-κB for their use (27), presumably because of the inducibility of this transcription factor and because of its ability to regulate cell cycle, DNA replication, and apoptosis. Consistent with this, inhibition of NF-κB blocked the ability of herpes simplex virus to replicate (28). Most viruses encode proteins that are capable of activating NF-κB. For example, the LMP-1 protein of Epstein-Barr virus activates NF-κB (29) in a manner similar to the mechanism used by the TNF receptor (30). Thus, NF-κB activation by viral infection is required for viruses to induce proliferative responses, to replicate their genetic material, and to induce pathogenic responses. The various roles for NF-κB in virus-associated mechanisms and pathology are discussed in the Perspective by Hiscott and his colleagues.

A relatively recent observation is that NF-κB is a critical regulator of apoptosis. Studies in this area were based on the original findings of Beg, Baltimore, and colleagues (31), who showed that the p65/RelA knockout mouse died embryonically from extensive liver apoptosis. In response to many normal physiological stimuli (such as TNF), NF-κB is activated and suppresses apoptotic potential through the transcriptional activation of genes whose products block apoptosis (reviewed in ref. 32). The involvement of NF-κB with

apoptosis has significant disease implications, as discussed below. Curiously, NF-κB has been found to be associated with antiapoptotic as well as proapoptotic mechanisms (32). For example, NF-κB activation appears to induce apoptosis in cells exposed to hydrogen peroxide (33). Consistent with the latter observation and with evidence that reactive oxygen species activate NF-κB, loss of one of the NF-κB subunits can block cell death in an ischemia/reperfusion stroke model (34). In these regards, NF-κB can be most easily viewed as a stress response factor that controls whether a cell will live or die. The nature (or strength) of the stimulus and the cell type involved may determine whether NF-κB leads to cell survival or cell death. In one of the Perspectives in this series, I discuss in more detail the complex roles of NF-κB in apoptosis.

NF-κB and NF-κB–like factors have been described in the nervous system (35). Importantly, NF-κB appears to control nervous system development, and its regulation is controlled by neurotransmitters and neurotrophic factors. Consistent with its role in regulating apoptosis, NF-κB serves a cell survival role in neurons in response to cell injury through the upregulation of antiapoptotic and antioxidant genes. The complex roles of NF-κB in the neurons and the potential pharmacological intervention in specific diseases, such as Alzheimer's disease and stroke, are discussed in the Perspective by Mattson and Camandola.

Several reports demonstrate that NF-κB is activated by oncoproteins, including oncogenic forms of Ras as well as viral oncoproteins, such as LMP-1 of Epstein-Barr virus and HTLV-I Tax (reviewed in refs. 36–38). More recently it has been shown that NF-κB is required for several of these oncoproteins to induce cellular transformation. Inhibition of NF-κB blocks cell transformation induced by oncogenic Ras and blocks tumor formation induced by Bcr-Abl (see ref. 36). NF-κB likely participates in oncogenesis both by suppressing apoptosis and by inducing cell proliferation. Thus, activation of NF-κB by oncogenic Ras suppresses Ras-induced apoptosis. Inhibition of NF-κB in conjunction with oncogenic Ras expression leads to apoptosis (39). The ability of NF-κB to control cell proliferation depends in part on its ability to transcriptionally activate cyclin D1 expression (36).

Because apoptosis is the primary mechanism of tumor cell killing by radiation and by chemotherapy, the observations that the activation of NF-κB by TNF suppresses apoptotic potential generated interest in the effect of NF-κB on the efficacy of cancer therapies. Indeed, suppression of NF-κB activation significantly enhances cell killing in culture in response to these treatments (40). In tumor models, NF-κB is activated in tumor cells in response to chemotherapy, and inhibition of NF-κB by viral expression of IκB (41) or by a small molecule inhibitor of NF-κB leads to significant enhancement in the apoptotic response of the chemotherapy (J. Cusack, R. Liu, and A. Baldwin, Jr., unpublished observations). In fact, complete elimination of experimental tumors can be achieved with optimal dosing regimens. The relevance of inhibition of NF-κB as an adjuvant approach to cancer therapy is covered in my Perspective on NF-κB and oncogenesis.

The experimental results outlined above and this Perspective series indicate that NF-κB is a primary effector of human disease. For this reason, numerous efforts are underway to develop safe inhibitors of NF-κB to be used in treatment of both chronic and acute disease situations. Many scientists question whether a factor that is required for basic immune responses can be effectively targeted to inhibit associated disease characteristics. Clearly, the most logical use of NF-κB inhibitors will be in acute situations, where short-term therapy is needed. Thus, inhibition of NF-κB during stroke or in cancer treatment would provide the least likelihood of side effects targeting immune function. However, the fact that long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) or glucocorticoids can be tolerated and that these compounds block NF-κB provides evidence that long-term use of NF-κB inhibitors is a valid strategy. The development of specific NF-κB inhibitors should reduce side effects associated with drugs such as NSAIDs and glucocorticoids and offer significant potential for the treatment of a variety of human diseases.

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